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PATENT- OG VAREMÆRKESTYRELSEN

TITLE

A Hydrogel

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a cross-linked hydrogel and the preparation a hydrogel, a solution for the preparation of a hydrogel and a hydrogel sheet.

Background of the Invention

Free radical, network-producing polymerizations are used in a variety of applications including coatings, information storage systems, films, and aspherical lenses and biomaterials.

Cross-linked hydrogels are commonly prepared by free radical polymerization. Over the past three decades, a number of hydrogels differing in structure, composition, and properties have been developed. Hydrogels are insoluble, water-swollen networks composed of hydrophilic homo-or copolymers. They are desirable for biomedical applications because of their high water content and rubbery nature, similar to natural tissue.

Free radical polymerization processes are initiated by free radical initiators to obtain ensure proper polymerization rates. These free radical initiators are activated by irradiation e.g. in the form of E-beam, microwaves, gamma or light (which includes UV, visible or near infrared). Thermal initiation is another widespread method of initiating free radical polymerization.

While all initiation methods have their advantages/disadvantages the use of photopolymerization is recognized as a fast, convenient and controllable way of preparing hydrogels through free radical polymerization. The polymerization process can be carried out under ambient or physiological conditions and even in the presence of biologically active materials. There are other advantages of using the photopolymerization technique for biomaterials. In general, the process is

benign and the process may also proceed rapidly at ambient conditions for most monomers and conventional initiators, i.e. fast curing rates. In addition, the ability to direct exposure of for example UV light and time of incidence to achieve spatial and temporal control is particularly advantageous for the formation of complex devices.

Due to their biocompatibility, permeability, and physical characteristics, hydrogels are suitable for use in many medical applications, including tissue engineering. Hydrogels may be useful for manipulation of tissue function or for scaffolds for tissue regeneration or replacement. The use of photopolymerization in the preparation of hydrogels is advantageous in comparison with conventional cross-linking methods because liquid hydrogels precursors can be delivered and cross-linked to form hydrogels in situ in a minimally invasive manner. This process also gives one spatial and temporal control over the conversion of a liquid to a gel, so that complex shapes can be fabricated. Hydrogels can be formed with varying polymer formulations in three-dimensional patterns since sequentially polymerized layers will firmly adhere to one another.

Photopolymerized hydrogels can be designed to degrade via hydrolytic or enzymatic processes and can be modified with biofunctional moieties within their structure to manipulate cell behaviour and to generate organ-specific tissue formation. These photopolymerizable hydrogels can be used as barriers, localized drug delivery depots, cell encapsulation materials, and scaffold materials. Other biomedical applications include the prevention of thrombosis, post-operative adhesion formation, drug delivery, coatings for biosensors, guide-wires and catheters, and for cell transplantation.

Visible or UV light can interact with light sensitive compounds called photo-initiators to create free radicals that can initiate polymerization to form cross-linked hydrogel (3-D polymeric networks). In vivo this principle has been utilized to polymerize or cure materials in dentistry to form sealant and dental restorations in situ. Photopolymerizations has also been used in electronic

materials, printing materials, optical materials, membranes, polymeric materials, and coatings and surface modifications.

Photopolymerization has several advantages over conventional polymerization techniques. These include spatial and temporal control over polymerization, faster curing rates (less than a second to a few minutes) at room or physiological temperature, and minimal heat production. Furthermore, photopolymerization can be utilized to create hydrogels in situ from aqueous precursors in a minimal invasive manner. Fabrication of polymers in situ is attractive for a variety of biomedical applications because this allows one to form complex shapes that adhere and conform to tissue structures, for example laparascopic devices, catheters, or subcutaneous injection with transdermal illumination.

Polymerizations conditions for in vivo applications are however difficult since biological systems require a narrow range of acceptable temperatures and pH, as well as absence of toxic materials such as monomers and organic solvents is demanded. Some photopolymerizations systems may overcome these limitations because the polymerization conditions are sufficiently mild (low light intensity, short irradiation time, physiological temperature, and low organic solvent levels) to be carried out in the presence of cells and tissues.

Photopolymerization schemes generally use a photoinitiator that has a high absorption at a specific wavelength of light to produce radical initiating species. Other factors that should be considered include its biocompatibility, solubility in water, stability, and cytotoxicity. Various photoinitiators have been investigated to achieve better photopolymerization. Photoinitiation is classified in three major classes depending on the mechanism involved in photolysis. The classes are radical photopolymerization trough 1) photocleavage, 2) hydrogen abstraction and 3) cationic photopolymerization. Cationic photoinitiators are generally not utilized in tissue engineering applications because they generate protonic acids and toxic side products. Cationic photopolymerization will not be discussed further here.

In radical photopolymerization by photocleavage, the photoinitiators undergo cleavage at C-C, C-Cl, C-O, or C-S bonds to form radicals when exposed to light. Water-soluble photoinitiators include aromatic carbonyl compounds such as benzoin derivatives, benziketals, acetophenone derivatives, and hydroxyalkyl-phenones. Acetophenone derivatives that contain pendant acrylic groups have been shown to substantially reduce the amount of unreacted photoinitiator with no significant loss in the initiation efficiency. Acetophenone derivatives, such as, 2,2-dimethoxy-2-phenyl acetophenone, have been used as photoinitiators to form hydrogels from acrylated polyethylene glycol (PEG) derivatives in several biomaterial studies.

Radical photopolymerization by hydrogen abstraction: When subjected to UV irradiation, photoinitators such as aromatic ketones (i.e., benzophenone and thioxanthone) undergo hydrogen abstraction from an H-donor molecule to generate a ketyl radical and a donor radical. The initiation of photopolymerization usually occurs through the H-donor radical while the ketyl radical undergoes radical coupling with the growing macromolecular chains. The photoinitiator propyl thixanthone has been shown to be cytocompatible.

Effective photoinitiators are for example compounds such as benzophenone, acetophenone, fluorenone, benzaldehyde, propiophenone, anthraquinone, carbazol, 3 or 4-methylacetophenone, 3 or 4-methoxybenzophenone, 4,4'-dimethoxybenzophenone, allylacetophenone, 2,2'-diphenoxyacetophenone, benzoin, methylbenzoin ether, ethylbenzoin ether, propylbenzoin ether, benzoin acetate, benzoinphenyl carbamate, benzoin acrylate, benzoinphenyl ether, benzoyl peroxide, dicumyl peroxide, azo isobutyronitrile, phenyl disulphide, acyl phosphene oxide or chloromethyl anthraquinone as well as mixtures thereof.

Peroxy – compounds, i.e. compounds containing an –O-O- binding, where oxygen has the oxidation number –1 are known as strong oxidation agents. They are capable of producing free radicals in many environments. As such peroxy-

compounds have been utilized in free radical polymerizations as initiators of various kind, i.e. thermal, photo or redox initiation.

Persulfate (peroxydisulphate) is well known as an initiator of vinyl polymerization in aqueous systems. Thermal decomposition produces radical ions, which directly or indirectly cause chain propagation. M denotes a macromer or monomer unit.

$$S_2O_8^{2-} \rightarrow 2SO_4^{\bullet-}$$

$$SO_4^{\bullet-} + M \rightarrow {}^{\cdot}SO_4M\bullet$$

$$SO_4^{\bullet-} + H_2O \rightarrow HSO_4^{-} + HO\bullet$$

$$HO\bullet + M \rightarrow HOM\bullet$$

It is also well known that decomposition can be induced by the addition of reducing agents, such as ferrous ions:

$$Fe^{2+} + S_2O_8^{2-} \rightarrow Fe^{3+} + SO_4^{2-} + SO_4^{\bullet-}$$

Peroxydisulphates have commonly also been employed in irradiation polymerization processes like irradiation with γ rays. The photodecomposition of the peroxydisulphate ion in water or water/ethanol mixtures also produces sulphate ion radicals, which are potentially useful in various emulsion polymerization techniques. Peroxyphosphates have been shown to photopolymerize methyl methacrylate.

Another process concerned with the chemistry of peroxides has proven useful in free radical polymerization, namely the photo-Fenton reaction.
The photo-Fenton reaction has been largely applied in oxidative degradation of organic pollutants for water treatment and in some special cases depolymerization technique. The photo-Fenton reaction has also been described to

produce polymers from vinylpyrrolidone (VP) and copolymers hereof (copolymers of VP and MAA (methacrylic acid).

The photo-Fenton reaction is a process comprising two-interconnected steps. Firstly, hydrogen peroxide is decomposed into hydroxyl radicals by the presence of Fe^{2+}, which is oxidized to Fe^{3+}. In the dark the reaction is retarded after complete conversion of Fe^{2+} to Fe^{3+}. Irradiation of the system by UV-light (around 365 nm) results in photoreduction of Fe^{3+} to Fe^{2+}, which produce new hydroxyl radicals with hydrogen peroxide according to the first process or to an additional effect of direct peroxide photolysis. In the above mentioned polymerization process practically no polymerization occurred without light. Hence, to create a high enough concentration of hydroxyl radicals to initiate chain propagation light is necessary.

It is believed, that any free radical initiation system, especially free radical polymerizations carried out in aqueous solutions capable of generating soluble peroxides may be greatly enhanced by the addition of soluble metal ions capable of initiating the decomposition of the formed peroxides (redox process). These metal ions include iron and other transition metals having at least to readily available oxidation states.

Polymerization of monomers using visible or UV irradiation has been thoroughly investigated. While such systems may work well for many applications including many biomaterials, they generally cannot be utilized in tissue engineering because most monomers are cytotoxic. As a result, photopolymerizable hydrogels for tissue engineering have generally been formed from macromolecular hydrogel precursors. Such precursors are water-soluble polymers with two or more reactive groups. Examples of photopolymerizable macromers include PEG acrylate derivatives, PEG methacrylates derivatives.

Poly(ethylene glycol) is a non-toxic, water soluble polymer which resists recognition by the immune system. The term PEG is often used to refer to

polymer chains with molecular weights below 20.000 while poly(ethylene oxide) (PEO) refers to higher molecular weight polymers. PEG may transfer its properties to another molecule when it is covalently bound to said molecule. This may result in toxic molecules becoming non-toxic (as is the case with PEG-DMA which is non-toxic pegylated dimethacrylic acid) or hydrophobic molecules becoming soluble when coupled to PEG. It exhibits rapid clearance from the body, and has been approved for a wide range of biomedical applications. Because of the properties, hydrogels prepared from PEG are excellent candidates as biomaterials.

Polyvinyl alcohol (PVA) derivatives, and modified polysaccharides such as hyaluronic acid derivatives and dextran methacrylate have been described as useful macromolecular precursors.

Polyvinylpyrrolidone (PVP) is another useful candidate. Polymeric materials based on poly(N-vinyl-2-pyrrolidone) (PVP) and its copolymers have found intense applications as hydrogels and membranes used in drug delivery systems, adhesive formulations, and in photographic and lithographic coatings. The low chemical toxicity of PVP, its solubility in water and in organic solvents as well as its ability to complex with many kind of substrates like dyes, surfactants, and other polymers, have promoted its use as a protective colloid in pharmaceutical and cosmetic products.

2. Description of the Related Art

US Patent No. 5,410,016 discloses the development of photopolymerizable biodegradable hydrogels. The hydrogel comprises a macromer on which is grafted biodegradable units such as poly(alpha-hydroxy acid), poly(glycolic acid), poly(DL-lactic acid) and poly(L-lactic acid). Other useful materials includes poly(amino acids), poly(anhydrides), poly(orthoester), poly(phosphazines) or poly(phosphoester). Polylactones like poly(ε-caprolactone), poly(δ-valerolactone) or poly(λ-butyrolactone).

PVP is mentioned as a possible water-soluble region of the macromer. Acrylates, diacrylates, oligoacrylates,methacrylates,dimethacrylates, oligomethacrylates are mentioned as polymerizable regions of the macromer. The macromers are synthesized in organic solvents are photosensitive macromers prepared from these macromers. A combination of PEG-DMA and PVP is mentioned, the photoinitiators employed are commonly known. Peroxydisulphates may be used as thermal initiators.

US Patent Application No. 2001/0044482 discloses interpenetrating polymer network (IPN) compositions and a process for the manufacturing of hydrogel contact lenses. The polymeric material is prepared by polymerization of an unsaturated alkyl(meth)acrylate or its derivatives such as 2-hydroxyethyl methacrylate (HEMA) as the principle monomer, optionally vinyl containing comonomer(s) to enhance the resulting water absorbing capability, polymerizable multi-functional cross-linking agent(s), an irradiation initiator and/or thermal initiator, optionally other additives to impart the resulting hydrogel specific properties such as UV-blocking ability and handling colorants; in the presence of a soluble hydrophilic interpenetrating networking agent such as polyvinyl-pyrrolidone or poly-2-ethyl-2-oxazoline (PEOX) with a specific molecular weight. PVP is mentioned as IPN agent, PEG-DMA is mentioned as a cross-linker and photoinitiation or/and thermal polymerization is mentioned. UV or thermal initiation is used alone or in combination.
The hydrogels are prepared by mixing all the ingredients (dissolved in each other), subjecting the mixture to a short UV curing (minutes) followed by a longer thermal post curing (hours). The obtained dry gel is then hydrated after curing. The method of preparation is used in order to obtain a thorough curing process to secure that all monomers have been consumed in the curing process. The curing process is quite time consuming.

US Patent No. 5,005,287 discloses a process for forming and applying a hydrophilic coating cured by UV-light to a plastic or metal part either directly, or indirectly via plastic film, to safety razor or razor blade unit. The coating

comprises a water-soluble polymer or copolymer of PVP, at least one radically polymerizable vinyl monomer and a photoinitiator. Several vinylic monomers, mostly of the type acrylic acid or methacrylic acids are mentioned. Oligoethylene glycol bisacrylate is mentioned as a suitable cross-linker. A wide range of photoinitiators is mentioned. Water is mentioned as a polymerization solvent. The cured polymer layers are of 5-1000 µm thickness. Curing times are in seconds to minutes.

Thus, there is still a need for a hydrogel, which can be produced in a fast and simple manner, being non-toxic and producible in both thin and thick layers. Surprisingly, such a hydrogel has been achieved by the present invention.

SUMMARY OF THE INVENTION

It is the first object of the invention to prepare a cross-linked hydrogel in a fast and simple manner.

It is another object of the invention to prepare a non-toxic hydrogel.

It is further an object of the invention to prepare a hydrogel of various shapes and thickness.

The present invention relates to a cross-linked hydrogel, the preparation of such hydrogel, a stock solution for preparing a hydrogel and a hydrogel sheet material.

Detailed Description of the Present Invention

The invention relates to a method of preparation of a cross-linked hydrogel, said method comprises the steps of preparing an aqueous solution comprising one or more hydrophilic polymers, a cross-linking agent and a photoinitiator, subjecting said solution to irradiation and obtaining a cross-linked hydrogel, wherein the photoinitiator comprises a compound containing a peroxy-group.

The invention further relates to a composition for preparation of a cross-linked hydrogel by photopolymerization, said composition comprises an aqueous solution comprising one or more hydrophilic polymers, a cross-linking agent and a photoinitiator, wherein said photoinitiator comprises a compound containing a peroxy-group.

The invention still further relates to a cross-linked hydrogel comprising one or more hydrophilic polymers, a cross-linking agent and a photoinitiator, wherein said photoinitiator comprises a compound containing a peroxy-group, said hydrogel being cross-linked by photopolymerization.
The invention still further relates to a cross-linked hydrogel sheet comprising hydrophilic polymers, a cross-linking agent and a photoinitiator, said photoinitiator comprises a compound containing a peroxy-group, said hydrogel sheet being cross-linked by photopolymerization, wherein said sheet has a thickness of 10 μm to at least 2 cm.

The invention relates to a method for preparing a hydrogel (a three dimensional cross-linked hydrophilic copolymer network) in a fast, efficient photo-curing method. This is obtained using photo-polymerization in aqueous solution employing photopolymerizable water soluble hydrophilic polymers and cross-linking agents as hydrogel precursors and water soluble peroxy compounds as photoinitiators alone or in combination with co-initiators (such as photo-Fenton like catalysis). The resulting hydrogel network is a combination of a grafted copolymer and a cross-linked network.

The method according to the invention allows the preparation of a non-toxic and biocompatible stable hydrogel due to the use of safe and non-toxic constituents with a low content of residuals. Hydrogels with a broad range of properties including a varying degree of adhesiveness may be prepared.

Hence, the hydrogel according to the present invention may be prepared for a vast number of various fields such as wound dressings, controlled release (drug

delivery) devices including transdermal drug delivery devices, cosmetics, biosensors or electrodes, coatings or membranes. Included are hydrogels as skin adhesives and protectants for instance for ostomy and continence care.

Still further, the photopolymerization method offers a safe and convenient way of preparing a cross-linked hydrogel by simply mixing the constituents and curing the solution in a free radical bulk solution photopolymerization process under ambient conditions. The hydrogel according to the invention may be prepared in industrial scale via a simple in-line process or it may be prepared in situ under physiological conditions (in vivo or in vitro). The use of the photopolymerization method according to the invention allows hydrogels to be prepared both in stock rolls and in complex shapes using moulding. Due to the photopolymerization technique employed in this invention it is possible to obtain deep curing of polymer solutions obtaining hydrogels of various thickness from very thin (μm) to very thick layers (several centimetres).

The method according to the invention allows the preparation of a non-toxic and biocompatible hydrogel through the use of safe and non-toxic constituents. The resulting hydrogel has very low content of residuals and may be used for biological or medical purposes without the need of drying, washing and rehydration to remove any undesired content of residuals.

A preferred embodiment of the invention relates to a cross-linked hydrophilic polymer network system, said hydrogel comprising a hydrophilic water-soluble polymer PVP or copolymers of PVP, cross-linked with a suitable cross-linking agent.

The hydrogel is prepared in aqueous solution through a free radical bulk solution polymerization using photopolymerization with wavelengths from 190-1000 nm, preferably 200-700nm. The polymerization is brought about by the decomposition of a water-soluble photoinitiator into free radicals, which directly or indirectly cause chain propagation. The critical property of the photoinitiating system is that

the polymerization will not proceed at a useful rate without the presence of the initiator.

The photocuring method described in the present invention is surprisingly fast and efficient. The hydrophilic polymers, the cross-linking agent and the photoinitiator are mixed in an aqueous solvent and cured by light obtaining a water containing cross-linked hydrogel system. The curing is rapid in the range of seconds to minutes depending of the desired thickness of the hydrogel. Deep complete curing can be obtained allowing very thick layers (several centimetres) of hydrogel to be prepared.

The method of the present invention is superior to common photopolymerization processes due the capability of a very effective deep curing (μm – several centimetres) in a short period of time (seconds to minutes) in solutions containing from a very low to a very high amount of water. The photocuring may be carried out in air under ambient temperature and pressure.

UV initiated photopolymerizations are often slow in air compared to in an inert atmosphere. However, the photopolymerization process according to the invention is seemingly not impaired by the presence of oxygen. Oxygen, which often inhibits free radical reactions, which inhibit propagation, does surprisingly not slow down the polymerization process in the in method according to the invention to any critical extent and the insensibility to oxygen contributes to an efficient curing. The time required for gelation is short (seconds to minutes depending on thickness). This is very significant. No significant difference in the polymerization rates and the physical/mechanical properties of the hydrogel is observed in hydrogels produced in air compared to hydrogels prepared in an inert atmosphere created by purging the solutions with nitrogen. However, to minimize the effect of any created peroxides due to dissolved oxygen in the aqueous solutions, which potentially could influence the stability of the resulting hydrogel, Fe^{2+} was added alone or in combination with one or more antioxidants like ascorbic acid to enhance the free radical initiating system.

Further distinctions from other systems using UV-curing free radical polymerization and peroxydisulphates or the ferrous co-initiator system may be made. For example it should be noted that it is not possible to obtain a strong gel network in the following cases:

a) By thermal initiation, i.e. introducing the aqueous solution to heat (80°C) in the same time span as in which the aqueous solutions is irradiated with UV-light. A thermal initiated gelation with peroxydisulphate would usually have a time span of hours,

b) by decomposition of the peroxydisulphate with a ferrous ion into sulphate radicals. The presence of a redox system like ascorbic acid and Fe^{2+} together with peroxydisulphate is not enough to create a useful and satisfying hydrogel network. It is necessary to irradiate the polymer solution with light simultaneously to obtain a strong cross-linked hydrogel,

c) by leaving out the cross-linking agent. Peroxydisulphate cross-linked PVP gels have been described using either thermal initiated polymerization or irradiation (γ rays). Furthermore, it has been described that aqueous PVP solutions could be directly cross-linked by irradiation with γ rays. In the present method no curing is seen when either PEG-DMA or peroxydisulphate or both are left out of the solution. Both are necessary for the formation of strong but soft hydrogel material.

When replacing the peroxydisulphates with other commonly used water-soluble photoinitiators and curing under identical conditions only a partly (surface) cured hydrogel may be obtained.

The hydrophilic polymers may be selected from the group of cellulose derivatives, polysaccharides, polyvinyl-pyrrolidone, polyvinyl alcohol, polyacrylic acid, poly (methyl vinyl ether/ maleic anhydride), poly (meth)acrylic acid, polethylenglycols (PEG), polyamides, polyacrylic amides, polyethylene glycol (PEG) or copolymers or blends of these.

A primary issue for the hydrophilic polymer is toxicity and water solubility. For all biologically related uses toxicity must be low or absent in the finished hydrogel. Thus, the hydrophilic polymers should not be harmful and should be non-toxic.

In a preferred embodiment of the invention the hydrophilic polymers comprise polyvinyl pyrrolidone (PVP) or PVP based copolymers.

The principle hydrophilic polymer is preferably polyvinyl pyrrolidone (PVP) or PVP based copolymers in order to obtain a hydrophilic, water-soluble polymer backbone. The amount of polymer used is preferably in the range 1-90 % w/w more preferred in the range of 5-50 % w/w, depending on the water content and other desired properties of the resulting hydrogel.

The cross-linking agent may comprise vinylic or unsaturated macromers or monomers such as mono-/di- or multifunctional acrylates or methacrylates.

The term "cross-linking agent" is used herein in a broad sense in that it is a composition, which is capable of providing cross-linking of the polymeric backbone, either by solely catalysing a cross-linking reaction or by becoming a part of the resulting polymeric network.

Typically, the cross-linkers are di- or multifunctional compounds that can incorporate themselves into the resulting polymer backbone during the polymerization process. The cross-linking agent may comprise vinylic or unsaturated macromers or monomers.

The concentration of the cross-linking agent is chosen according to the required degree of cross-linking, and consequently it is determined not only by the amount of the cross-linking agent but also by the type and ability to form the cross-linked polymer. The less effective cross-linking agents have to be applied in a higher concentration than the more effective ones. While the cross-linker in principle

could be added in very high concentrations up to approximately 80 %, preferably, the cross-linking agents may be present up to 10 – 15 % by weight.

The cross-linking agent may include, but are not being limited to, cyclic or open-chain ether groups, such as esters of single or multiple ethoxylated or propoxylated C.sub.1 -C.sub.20 alcohols, tetrahydrofuran ("THF") carbinol acrylate or THF carbinol methacrylate, hydroxyalkyl esters, such as 2-hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, 2-hydroxypropyl acrylate or 2-hydroxypropyl methacrylate, N,N-dimethylamino-2-hydroxyethyl acrylate, N,N-dimethylamino-2-hydroxyethyl acrylate, N,N-dimethylaminoethyl methacrylate or salts thereof, such as N,N,N-trimethylammonium-2-ethyl methacrylate chloride, also acrylamide, N-alkylacrylamide with 1-10 C atoms in the alkyl group, N-2-hydroxyethyl acrylamide, N-2-hydroxypropyl acrylamide or methacrylamide, N-2-hydroxyethyl methacrylamide, N-2-hydroxypropyl methacrylamide, acrylonitrile and methacrylonitrile.

Suitable di- or multifunctional cross-linking agents may be, but not being limited to ethylene glycol dimethacrylate, triethylene glycol dimethacrylate, tetraethylene glycol dimethacrylate, trimethylopropane trimethacrylate, bisphenol A dimethacrylate, ethoxylate bisphenol A dimethacrylate, pentaerythritol tri- and tetrametacrylate, tetramethylene dimethacrylate, methylenebisacrylamide, methacryloxyethyl vinyl carbonate, triallylcyanurate, methacryloxyethyl vinyl urea, divinyl benzene, diallyl itaconate, allyl methacrylate, diallyl phtalate, polysiloxanylbisalkyl methacrylate and polyethylene glycol dimethacrylate.

Oligo- or macromeric structures of a non-toxic nature are preferred. Of these, PEG containing di- or multifunctional oligo-or macromers may be of special interest. In the present invention, polyethylene glycol dimethacrylate of an approximately molecular weight of 400 (PEG-DMA 400) and an approximately molecular weight of 1000 (PEG-DMA 1000) may be preferred as cross-linking agent.

In a preferred embodiment of the invention the photoinitiator comprises inorganic peroxydisulphates, such as sodium, potassium or ammonium peroxydisulphate.

The solution may further comprise one or more co-initiators or redox initiators. The co-initiator may be in the form of transition metal ions.

Addition of a redox system such as Fe^{2+} /ascorbic acid may further enhance the initiation of polymerization.

Metal ions suitable for use as co-/redox-initiators may be any of the transition metal ions, having at least two readily oxidation states. These include but are not being limited to ferric/ferrous, cupric/cuprous, ceric/cerous, cobaltic/cobaltous, vanadate(V)/vanadate(IV), permanganate and manganic/manganous.

Surprisingly, it is possible to obtain the fast and deep efficient curing of the described polymer system by photodecomposition by UV-light using an initiator, which until now has found most use as a thermal/redox initiator, i.e. a water-soluble inorganic peroxydisulphate. This curing system can be used alone or in combination with a ferrous co-initiator system (photo-Fenton like) as a redox-initiating system, which will enhance the initiation process by creating more free radicals initiation species.

The photoinitiators may be water-soluble peroxy-group containing compounds, preferably, but not being limited to the inorganic peroxydisulphates, such as sodium, potassium or ammonium peroxydisulphate, used alone or in combination with a co-initiator preferably Fe^{2+}. The peroxydisulphates are photodecomposed to sulphate radicals, which radicals initiate the cross-linking process by creating PVP-polymer radicals and PEG-DMA radicals. Photoinitiators may be used in the polymer mixture in an effective quantity from 0.1 to 5% w/w, in particular 0.5 to 5% w/w. Addition of a co-initiator like Fe^{2+} may give a higher initial concentration of free radicals. Addition of a redox system like Fe^{2+} /ascorbic acid enhances the initiation of polymerization. Also, the stability of the hydrogel may be further

improved by the addition of Fe^{2+}, Fe^{2+} /ascorbic acid or the like. These systems may initiate the decomposition of peroxides which could be formed during the polymerisation process and which possibly could impair hydrogel stability.

As the present invention is based on photocuring in an aqueous environment a water-soluble photoinitiating system is preferred. However, any compound, which disintegrates into radicals when subjected to radiation may be used. A primary concern of choice is the toxic profile of the photoinitiator.

The photoinitiator system in the present invention may in principle be used in combination with known water-soluble photoinitiators such as benzophenone, acetophenone, fluorenone, benzaldehyde, propiophenone, anthraquinone, carbazol, 3 or 4-methylacetophenone, 3 or 4-methoxybenzophenone, 4,4'-dimethoxybenzophenone, allylacetophenone, 2,2'-diphenoxyacetophenone, benzoin, methylbenzoin ether, ethylbenzoin ether, propylbenzoin ether, benzoin acetate, benzoinphenyl carbamate, benzoin acrylate, benzoinphenyl ether, benzoyl peroxide, dicumyl peroxide, azo isobutyronitrile, phenyl disulphide, acyl phosphene oxide or chloromethyl anthraquinone as well as mixtures thereof.

Co-catalysts such as amines, for example triethanolamine, as well as other trialyl amines of trialkylol amines could be added. In principle, any compound typically used in in photoinitiation as radical generators or cocatalysts may be used. Sulphur compounds, heterocycles, for example, imidazole, enolates, organo-metallics and other compounds, such as N-phenyl glycine.

Additionally, comonomers could be added to change the polymerization process or the final properties of the hydrogel of the invention. These comonomers include sulphoxide containing methacrylate, polyethylene glycol (400) ether monomethacrylate and glycerol monomethacrylate. Also of interest are N-vinyl compounds, including N-vinylpyrrolidone, N-vinyl acetamide, N-vinyl imidazole, N-vinyl caprolactam and N-vinyl formamide. A primary concern when including a cocatalyst or a comonomer is the toxicity in the resulting hydrogel system.

The solvent of choice for the preparation of the cross-linked hydrogel in the present invention is water or buffered aqueous solutions. However, any solvent, which may have a favourable effect on the photopolymerization process or the working properties of the hydrogel system may be employed. Suitable solvents may be acetone, methyl ethyl ketone, methanol, ethanol, propanol, butanol, ethyl acetate, butyl acetate, methylene chloride, toluol, THF, water and mixtures thereof. Again, the concern of any potential residual solvent toxicity in the finished hydrogel is determining the choice of co-solvent. Water is preferred as solvent due to the non-toxic properties, as well as no washing or extraction of any toxic solvent from the resulting hydrogel may be needed, when water is employed.

In one embodiment of the invention the hydrogel comprises one or more plasticizers, preferably polyols. The plasticizers include, but are not being limited to polyols like glycerol, propylene glycol and polyethylene glycols of various chain lengths.

The hydrogels may be prepared with a range of additives to obtain special chemical or physical characteristics. Surfactants may be added for stabilization purposes.

Polymeric material may be added for viscosity improvement of the polymer solutions: Cellulose derivatives, like methyl cellulose, hydroxymethylcellulose, hydroxypropyl cellulose, ethyl cellulose, sodium carboxymethyl cellulose, other polysaccharides like but not being limited to acacia gum, trachagant, alginate, carrageenan, xanthan, locust bean gum, chitosan, starch derivatives like carboxymethyl-starch or dextran.

Synthetic polymers which introduces complexation with the principle polymers in the present invention may also be utilized to alter the photocuring polymer solutions and include but are not being limited to polyacrylates and polymethacrylates. Solubilizers like cyclodextrins may also be added.

The gels may be provided with a supporting net or reinforcing layer. The reinforcing layer may ease the handling of the hydrogel as well as the strength of the gel is enhanced. The reinforcing layer may be in the form of a web or a net, or a non woven material such as polyester, polyamide polyethyl or polypropyl, fibres, woven fabrics such as gauze, or foils or films with an open space structure or the like. The reinforcing layer may be incorporated in the hydrogel, or the hydrogel may be laminated or casted onto the net.

The hydrogel may be provided with a backing layer. The backing layer may be totally occlusive, liquid impervious but vapour permeable or it may be of a type having a higher water permeability when in contact with liquid water than when not in contact. The backing layer may be of any suitable material known per se for use in the preparation of medical devices e.g. a foam, a nonwoven or a polyurethane, polyethylene, polyester or polyamide film.

A suitable material for use as a backing layer is a polyurethane. A preferred low friction film material is disclosed in US patent No. 5,643,187.

In one embodiment of the invention the hydrogel of the present invention is conductive. This is obtained by adding electrolytes like various kinds of inorganic salts or other conductive compounds.

The hydrogel according to the invention may comprise one or more active ingredients.

The hydrogel according to the invention may comprise one or more active ingredients, e.g. pharmaceutically active compounds.

The compounds may be immobilized on or within the hydrogel. Numerous techniques exist including physical entrapment, electrostatic attraction, physical adsorption or absorption and chemical bonding may be utilized.

The active compound may be entrapped by conducting the photopolymerization of the polymer solutions in the presence of the active compound. Alternatively, the active agent could be introduced after curing by imbibition. In imbibition, the previously prepared hydrogel is placed in a solution containing the solute for an extended period of time. Eventually, the solute diffuses into the hydrogel.

Examples of such pharmaceutical medicaments includes a cytochine such as a growth hormone or a polypeptide growth factor such as TGF, FGF, PDGF, EGF, IGF-1, IGF-2, colony stimulating factor, transforming growth factor, nerve stimulating growth factor and the like giving rise to the incorporation of such active substances in a form being apt to local application in a wound in which the medicament may exercise its effect on the wound, other medicaments such as bacteriostatic or bactericidal compounds, e.g. iodine, iodopovidone complexes, chloramine, chlorohexidine, silver salts such as sulphadiazine, silver nitrate, silver acetate, silver lactate, silver sulphate, silver sodium thiosulphate or silver chloride, zinc or salts thereof, metronidazol, sulpha drugs, and penicillin's, tissue-healing enhancing agents, e.g. RGD tripeptides and the like, proteins, amino acids such as taurine, vitamins such ascorbic acid, enzymes for cleansing of wounds, e.g. pepsin, trypsin and the like, proteinase inhibitors or metalloproteinase inhibitors such as Illostat or ethylene diamine tetraacetic acid, cytotoxic agents and proliferation inhibitors for use in for example surgical insertion of the product in cancer tissue and/or other therapeutic agents which optionally may be used for topical application, pain relieving agents such as lidocaine or chinchocaine, emollients, retinoids or agents having a cooling effect which is also considered an aspect of the invention.

The active ingredient may also comprise odour controlling or odour reducing material.

MATERIALS AND METHODS

Example 1

20 g of polyvinyl-pyrrolidone (PVP K90) was mixed with 4 g of polyethylene-glycol dimethacrylat 1000 (PEG-DMA 1000) and 1 g natriumperoxidisulfate in 75 g of 0.1 M citric acid/citrate buffer pH 6.0. The polymer solution was dispensed into a suitable mold in 5 mm thickness and cured under UV-light. The hydrogel was UV-cured under a single UV-lamp (specifications: 200 W/cm, microwave powered "D"-spectral type lamp with a conveyor speed of 0.4 m/min). A sheet hydrogel of 5 mm thickness was obtained.

The rheological properties of the gel was examined using dynamic oscillation rheology determining the viscoelastic moduli, G' (Elastic modulus) and G" (Loss modulus) and tan delta (G"/G') at a frequency of 1 Hz, 25°C.

The equilibrium swelling was determined by swelling the cured hydrogels in Milli-Q water for 24 hours and calculating the relative increase in uptake of water.

The viscoelastic moduli of this hydrogel was
G' = 4588 Pa, G" = 1110 Pa and tan delta = 0.242
Equilibrium swelling = 700 %

Example 1 describes the preparation of a basic hydrogel of the invention. It is seen that at hydrogel containing 75 % water w/w is obtained with a high elastic moduli, a lower G" which gives a tan delta value indicating a quite elastic system. Despite the high amount of water the hydrogel is still capable of absorbing water 7 times its own weight.

Example 2

20 g of polyvinyl-pyrrolidone (PVP K90) was mixed with 4 g of polyethylene-glcyol dimethacrylat 1000 (PEG-DMA 1000) and 1 g natriumperoxidisulfate in 60 g of

0.1 M citric acid/citrate buffer pH 6.0. To this solution was added 10 ml of 5.0 x 10^{-4} M $FeSO_4$ and 5 ml of 1 x 10^{-3} M ascorbic acid. The polymer solution was dispensed into a suitable mold in 5 mm thickness and cured under UV-light. The hydrogel was UV-cured under a single UV-lamp (specifications: See Example 1). A sheet hydrogel of 5 mm thickness was obtained.

Rheological characterization as in Example 1.
G' = 5300 Pa, G" = 1200 Pa and tan delta = 0,226
Equilibrium swelling = 625 %

The use of a co-initiator system for a possible improvement of curing of the hydrogel was examined. As a higher elastic modulus (G'), a lower tan delta and a lower equilibrium swelling is observed, this implies a stronger and more cross-linked gel which is a result of a better curing.

Example 3

10 g of polyvinyl-pyrrolidone K90 (PVP K90) is mixed with 10g polyvinyl-pyrrolidone K25 (PVPK25), 4 g of polyethylene-glycol dimethacrylat 1000 (PEG-DMA 1000) and 1 g natriumperoxidisulfatein 75 g of 0.1 M citric acid/citrate buffer pH 6.0. The polymer solution was dispensed into a suitable mold in 5 mm thickness and cured under UV-light. The hydrogel was UV-cured under a single UV-lamp (specifications: See Example 1). A sheet hydrogel of 5 mm thickness was obtained.

Rheological characterization as in example 1.
G' = 2400 Pa, G" = 630 Pa and tan delta = 0,262
Equilibrium swelling = 800 %

Examples 3 shows the use of shorter chained PVP in combination with the principle PVP K90 macromer. This produces a more soft gel compared to the

basic hydrogel and with a higher swelling ratio. Also the tackiness of the gel is increased.

Example 4

20 g of polyvinyl-pyrrolidone-co-vinylacetat (VA64) is mixed with 4 g of polyethylene-glycol dimethacrylat 1000 (PEG-DMA 1000) and 1 g natriumperoxidisulfate in 60 g of 0.1 M citric acid/citrate buffer pH 6.0. The polymer solution was dispensed into a suitable mold in 5 mm thickness and cured under UV-light. The hydrogel was UV-cured under a single UV-lamp (specifications: See Example 1). A sheet hydrogel of 5 mm thickness was obtained.

Rheological characterization as in Example 1.
G' =2500, G" = 955 and tan delta = 0,382
Equilibrium swelling = 850 %

Example 4 describes the use of a water-soluble copolymer of vinylpyrrolidone and vinylacetat. Softness and tackiness are increased. Swelling is increased too.

Example 5

20 g of polyvinyl-pyrrolidone K90 (PVP K90) was mixed 4 g of polyethylene glycol dimethacrylat 1000 (PEG-DMA 1000) and 1 g natriumperoxidisulfate in 65 g of 0.1 M citric acid/citrate buffer pH 6.0. 10 g of glycerol was added to this solution. The polymer solution was dispensed into a suitable mold in 5 mm thickness and cured under UV-light. The hydrogel was UV-cured under a single UV-lamp (specifications: See Example 1). A sheet hydrogel of 5 mm thickness was obtained.

Rheological characterization as in Example 1.
G' = 3640 Pa G" = 1120 Pa and tan delta = 0,306
Equilibrium swelling = 850 %

Example 5 shows the addition of a polyol. The effect of this additive is a softer feel, an increase in tack, a higher degree of swelling as compared to the basic hydrogel in Example 1. The permeability and water loss is lowered.

Example 6

10 g of polyvinyl-pyrrolidone K90 (PVP K90) was mixed with 4 g of polyethylene glycol dimethacrylat 1000 (PEG-DMA 1000) and 1 g natriumperoxidisulfate in 60 g of 0.1 M citric acid/citrate buffer pH 6.0. To this solution was added 5 g of KCl. The hydrogel was UV-cured under a single UV-lamp (specifications: See Example 1). A sheet hydrogel of 5 mm thickness was obtained.

Rheological characterization as in Example 1.
G' = 2810 Pa, G" = 1070 and tan delta = 0,380
Equilibrium swelling = 725 %

Example 6 shows a basic hydrogel with the addition of an electrolyte to produce a conductive hydrogel for possible use in electrodes. Compared to the basic hydrogel in Example 1, the presence of 5 % w/w of KCl makes the resulting gel softer and a little less elastic. However, the hydrogel has a bit more preferred tack.

Example 7

Cytotoxicity Test

A hydrogel prepared according to example 1 was tested for cytoxicity according to ISO standard 1993-5 described in USP 24 "elution assay".

No cell toxicity was observed.

Example 8

Residual PEG-DMA

A hydrogel prepared according to Example 1 was tested for residual PEG-DMA (MAA). The gel was swollen in water in a vial and homogenized in this vial. The vial was centrifuged and the supernatant was analyzed for MAA via a reesterification-process and HS-GCMS. The amount of PEG-DMA is < 25ppm (5 ppm MAA-equivalents).

Example 9

A multilayer hydrogel

A hydrogel was prepared according to Example 1. A polymer solution according to Example 4 was placed on the hydrogel and cured under the same standard conditions UV-light. A further layer consisting of the polymer solution described in Example 5 was then put on the top and cured creating a three-layered gel structure.
This multilayer gel having three different swelling zones may be utilized as drug delivery vehicle for the controlled release of a pharmacological active compound.

Example 10

Hydrogel with incorporated support.

A hydrogel according to Example 1 was prepared incorporating a foil of an open space structure. The foil was placed directly in the polymer solution, which was

then cured according to Example 1. It was possible to cure the polymer solution with net directly to obtain hydrogel with incorporated supporting foil.
Such a hydrogel system may be suitable for use in wound care, for example for burn wounds.

Example 11

Hydrogel with a backing layer

A polymer solution according to Example 1 was prepared and placed on a polyurethane (PU) film. The polymer solution was cured in accordance to Example 1 and a resulting hydrogel immobilized on the PU-film was obtained, thus demonstrating that the hydrogel may be prepared and immobilized directly on a suitable surface.

Claims

1. A method of preparation of a cross-linked hydrogel, said method comprises the steps of preparing an aqueous solution comprising one or more hydrophilic polymers, a cross-linking agent and a photoinitiator, subjecting said solution to irradiation and obtaining the cross-linked hydrogel, wherein the photoinitiator comprises a compound containing a peroxy-group.

2. A method according to claim 1 characterised in that that the photoinitiator comprises peroxydisulphates, such as sodium, potassium or ammonium peroxydisulphate.

3. A method according to claim 1 or 2 characterised in that the solution comprises one or more co-initiators in the form of multivalent transition metal ions.

4. A method according to any of claims 1-3 characterised in that the hydrophilic polymer comprises cellulose derivatives, polysaccharides, polyvinyl pyrrolidone, polyvinyl alcohol, polyacrylic acid, poly (methyl vinyl ether/ maleic anhydride), poly (meth)acrylic acid, polethylenglycols (PEG), polyamides, polyacrylic amides,polyethylene glycol (PEG) or copolymers or blends of these.

5. A method according to any of claims 1-4 characterised in that the hydrophilic polymer comprises polyvinyl-pyrrolidone (PVP) or PVP based copolymers.

6. A method according to any of claims 1-5 characterised in that the cross-linking agent comprises vinylic or unsaturated macromers or monomers such as mono-/di- or multifunctional acrylates or methacrylates.

7. A method according to claim 1-6 characterised in that the solution comprises one or more plasticizers.

8. A composition for preparation of a cross-linked hydrogel by photopolymerization, said composition comprises an aqueous solution comprising one or more hydrophilic polymers, a cross-linking agent and a photoinitiator, wherein said photoinitiator comprises a compound containing a peroxy-group.

9. A cross-linked hydrogel sheet comprising hydrophilic polymers, a cross-linking agent and a photoinitiator, said photoinitiator comprises a compound containing a peroxy-group, said hydrogel sheet being cross-linked by photopolymerization, wherein said sheet has a thickness of 10 μm to 2 cm.

9. A cross-linked hydrogel comprising one or more hydrophilic polymers, a cross-linking agent and a photoinitiator, wherein said photoinitiator comprises a compound containing a peroxy-group, said hydrogel being cross-linked by photopolymerization.

10. A hydrogel according to claim 1 characterised in that the gel is conductive.

Abstract

A Hydrogel

A cross-linked hydrogel comprising one or more hydrophilic polymers, a cross-linking agent and a photoinitiator, wherein said photoinitiator comprises a compound containing a peroxy-group, said hydrogel being cross-linked by photopolymerization. The hydrogel will e.g. be suitable for use in medical devices such as wound dressings and the like.